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Disease-specific survival and locoregional control in tonsillar carcinoma

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Disease-specific survival and locoregional control in tonsillar carcinoma

In a nationwide survey on oropharyngeal carcinoma in the Netherlands (1986–1990), 380 patients with a tonsillar carcinoma were retrospectively studied. The records of 268 (71%) men and 112 (29%) women with a median age of 59 yr (range 31–91), who had squamous cell carcinoma (272 patients, 98%) or undifferentiated carcinoma (8 patients, 2%) were reviewed with respect to treatment, disease-specific survival and locoregional control. Distribution by stage according to the UICC'92 system was: 27 patients (7%) stage I, 59 (15%) stage II, 99 (26%) stage III, 182 (48%) stage IV and 13 patients (3%) unknown stage. Using a previously reported revised staging system the following distribution was obtained: 118 patients (31%) stage I, 120 (31%) stage II, 67 (18%) stage III, 54 (14%) stage IV and 21 patients (6%) with an unknown stage. Treatment consisted of radiotherapy alone in 231 patients (61%), surgery and radiotherapy in 101 (27%), surgery alone in 30 (8%), chemotherapy in 5 (2%) and 13 patients (3%) did not receive any treatment. At 5-yr the overall survival was 32%, the disease-specific survival 42% and the locoregional control 61%. In patients treated with radiotherapy alone the disease-specific survival was 39%, for surgery and radiotherapy 53% and for surgery alone 83%. The disease-specific survival according to UICC'92 stage was 71% in stage I, 59% in II, 50% in III and 32% in stage IV ($P < 0.0001$). In the revised staging the survival figures were 63% in stage I, 43% in II, 31% in III and 9% in IV ($P < 0.0001$). The two staging systems appeared to be comparable in prognostic discrimination; the clinical relevance of the revised stage might, however, be slightly superior to the UICC'92 version. The difference in results after radiotherapy alone and surgery + radiotherapy remained significant, also after adjusting for stage ($P < 0.0001$).

Keywords tonsillar carcinoma survival locoregional control

The tonsillar region is the most frequent site of cancer in the oropharynx.^{1–3} Despite the advanced stage of the disease at first presentation in the majority of patients,^{4–7} better treatment results are reported in these tumours,^{4–7} when compared

with two other subsites in the oropharynx, i.e. the base of the tongue,^{8–11} and the posterior oropharyngeal wall.^{12–15} Only soft palate lesions have a similar or slightly better prognosis than tonsillar cancers.¹⁵

The hypothesis that the subsite constitutes not only a separate clinical entity but also forms an independent prognostic factor in oropharyngeal carcinoma¹⁶ was recently tested in the frame of a nationwide study in the Netherlands on a group of

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Table 1. The revised staging system for oropharyngeal carcinoma.¹⁸ The T, N and M categories are identical as in the UICC'92/AJCC'88 system

Stage I	T 1-2	N 0-1	M 0
Stage II	T 1-2	N 2	M 0
	T 3	N 0-1	M 0
	T 4	N 0	M 0
Stage III	T 1-2	N 3	M 0
	T 3	N 2	M 0
	T 4	N 1	M 0
Stage IV	T 3	N 3	M 0
	T 4	N 2-3	M 0
	Any T	Any N	M 1

640 patients, treated between 1986 and 1990.¹⁷ In univariate analysis, tumours in the tonsillar region were associated with better survival. However, on multivariate analysis other factors, i.e. midline origin of the tumour, a revised staging system and sex, emerged statistically as more significant than the subsite.¹⁸

The revised staging system, mentioned here, comprises a modified combination of the existing TNM categories for this patient population (Table 1), which was compared with the current UICC'92/AJCC'88 staging system.¹⁹ This revised staging seems to provide a better prognostic discrimination for disease-specific survival. The relevance of the revised staging on different subsites in this series and/or on other large series remains to be verified, but it seems obvious that the present staging systems are not yet optimal.^{18,20,21}

In this paper carcinoma of the tonsillar region is studied as a single clinical entity. Treatment results in terms of survival and locoregional control are investigated and the effects of the revised staging system are further analysed.

Patients and methods

PATIENTS

As reported earlier,^{17,18} the study was conducted in seven major referral centres, participating in the Dutch Head and Neck Cooperative Oncology Group: the University Hospitals of Groningen, Leiden and Maastricht in combination with the Radiotherapeutic Institute Limburg, Nijmegen and Rotterdam in cooperation with the Dr Daniel Den Hoed Cancer Center, Utrecht, and The Netherlands Cancer Institute, in combination with the University of Amsterdam. In each participating centre the charts of patients admitted for oropharyngeal carcinoma between 1986 and 1990 were reviewed. Data related to epidemiology, staging, treatment and follow-up were collected using standardized checklists and returned as a hard copy to the Comprehensive Cancer Centre Amsterdam (IKA). There, a centralized data entry, using a scientific information retrieval (SIR) database, version 3.2, was performed. Patients who were admitted to more than one centre

were identified by cross-checking of epidemiological data, and the totals were adjusted accordingly.

The records of patients analysed previously were updated with respect to the data on locoregional control, resulting in a total of 653 patients with oropharyngeal carcinoma. The results of the 380 patients with tonsillar carcinoma are presented in this paper.

DEFINITIONS AND STATISTICAL ANALYSIS

Patients were followed for a minimum of 3 yr or until death. Treatment of patients with either residual locoregional tumour or a locoregional recurrence was considered a failure. Patients with distant metastases only were censored at the time of diagnosis of metastases. Other patients were censored at the time of death or at the end of the follow-up. Three analyses were performed.

- 1 Identification of possible predictors for locoregional control, using a backward elimination procedure of variables related to treatment, tumour and epidemiology. A detailed list of the variables has been published previously.¹⁸
- 2 Comparison of the three main treatment groups (radiotherapy alone, surgery and radiotherapy, and surgery alone) with respect to locoregional control, adjusted for the prognostic variables identified from the first analysis.
- 3 A test of the differences between patients treated by radiotherapy alone versus surgery and radiotherapy with respect to stage (UICC'92), by studying two-way interactions between treatment and stage.

In all multivariate analyses the proportional hazard model was used. *P*-values were calculated from the likelihood ratio statistics. Univariate curves were computed using the life table method with 1-month intervals or the product-limit method. Adjusted curves were calculated from the cumulative hazard function, estimated according to the method of Link.²² The variable for which the curves had to be calculated was used as stratum variable, whereas the variables that had to be adjusted for were included in the model as covariates. The curves were calculated at approximate mean values of the covariates in the whole group.

Results

The group of 380 patients with tonsillar carcinoma consisted of 268 (71%) men and 112 (29%) women with a median age of 59 (31-93) yr.

STAGING

Distribution by stage of the disease according to the UICC'92 system was: 27 patients (7%) stage I, 59 (15%) stage II, 99 (26%) stage III, 182 (48%) stage IV and 13 patients (3%) had

an unknown stage of the disease. Distribution by the revised staging system¹⁸ was: 118 patients (31%) in stage I, 120 (31%) in II, 67 (18%) in III, 54 (14%) in IV and 21 (6%) unknown.

TREATMENT AND SURVIVAL

Two hundred and ninety-eight patients (78%) were treated with intention to cure, 77 (20%) received palliative treatment and for five patients (2%) the intention to treat was not known in retrospect. The treatment corresponded to the standard protocol in operation in the participating centres in 325 patients (85%), was different from the standard in 52 patients (14%) and was unknown in the remaining three patients (1%). The main reasons for deviating from the standard treatment were poor general condition in 15 patients (4%) and refusal in 10 patients (3%); in all other patients but one (refusing standard treatment because of age), multiple reasons for deviating from the standard protocols were given.

Two hundred and thirty-one patients (61%) were treated with radiotherapy alone, 101 (27%) with surgery and radiotherapy, 30 (8%) with surgery alone, five patients (2%) with chemotherapy alone, and the remaining 13 patients (3%) did not receive any treatment. The group of 231 patients treated with radiotherapy alone also includes 27 patients who received primary radiotherapy but also underwent a neck dissection. These patients, the majority of whom had (UICC'92) stage III–IV disease will be discussed separately. The treatment modalities for stage UICC'92 and for the revised system are shown in Figure 1. In the revised staging system, surgery alone was used only in stages I–II and a steady relative increase of patients treated with radiotherapy alone was seen from 7% in stage I to 70% in stage IV. In the UICC'92 system, this distribution was less apparent, with a total of seven patients

(2%) in stages III–IV still receiving surgery as the only treatment modality.

At 5 yr the overall survival was 32% and the disease-specific survival 42%. As can be seen from Figure 2, the disease-specific survival in patients treated with radiotherapy alone was 39%, with surgery and radiotherapy 53%, and with surgery alone 83%.

The disease-specific survival in both staging systems, shown in Figure 3, ranged from 71% in stage I to 32% in stage IV ($P < 0.0001$) of the UICC'92 system and from 63% to 9% ($P < 0.0001$) in the corresponding stages of the revised system.

LOCOREGIONAL CONTROL

The status at the end of the follow-up is shown in Table 2. The locoregional control at 5 yr was 61%. By treatment modality the 5-yr figures were 54% for radiotherapy alone, 74% for surgery and radiotherapy, and 96% for surgery alone (Figure 4).

When analysed separately, the 27 patients who underwent neck dissection followed by radiotherapy to the primary site, appeared to have a 5-yr disease-specific survival of 48% and a locoregional control of 75%. Locoregional control by UICC'92 stage was: 92% in stage I, 75% in II, 66% in III and 47% in IV ($P < 0.0001$; Figure 5). In the revised staging system the corresponding figures were 78%, 65%, 43% and 25% ($P < 0.0001$; Figure 5).

ANALYSIS OF PROGNOSTIC VARIABLES FOR LOCOREGIONAL CONTROL

From the analysis of prognostic variables for locoregional control only the stage, UICC'92 or revised, emerged as being clearly important ($P < 0.0001$ throughout all steps). Due to a large overlap (high collinearity) of the two staging systems, including both systems in the multivariate analysis would reduce their prognostic value to clear non-significance. Therefore, most analyses were adjusted for UICC'92 staging only.

Adjusted for stage, there is ample evidence that patients treated with radiotherapy alone had a worse locoregional control than patients treated with surgery and radiotherapy ($P < 0.0001$, Figure 6). The 5-yr figures for the UICC'92 stages were 80% in stage I, 71% in stage II, 63% in stage III, and 40% in stage IV. In the revised staging these figures were 100%, 100%, 71% and 68%, respectively.

The 27 patients from the radiotherapy group who also underwent a neck dissection had a favourable locoregional control compared to other patients treated with radiotherapy alone throughout all steps of the analysis ($P = 0.036$).

Discussion

In this analysis a subset of 380 patients with tonsillar carcinoma, extracted from a larger group of 653 patients with

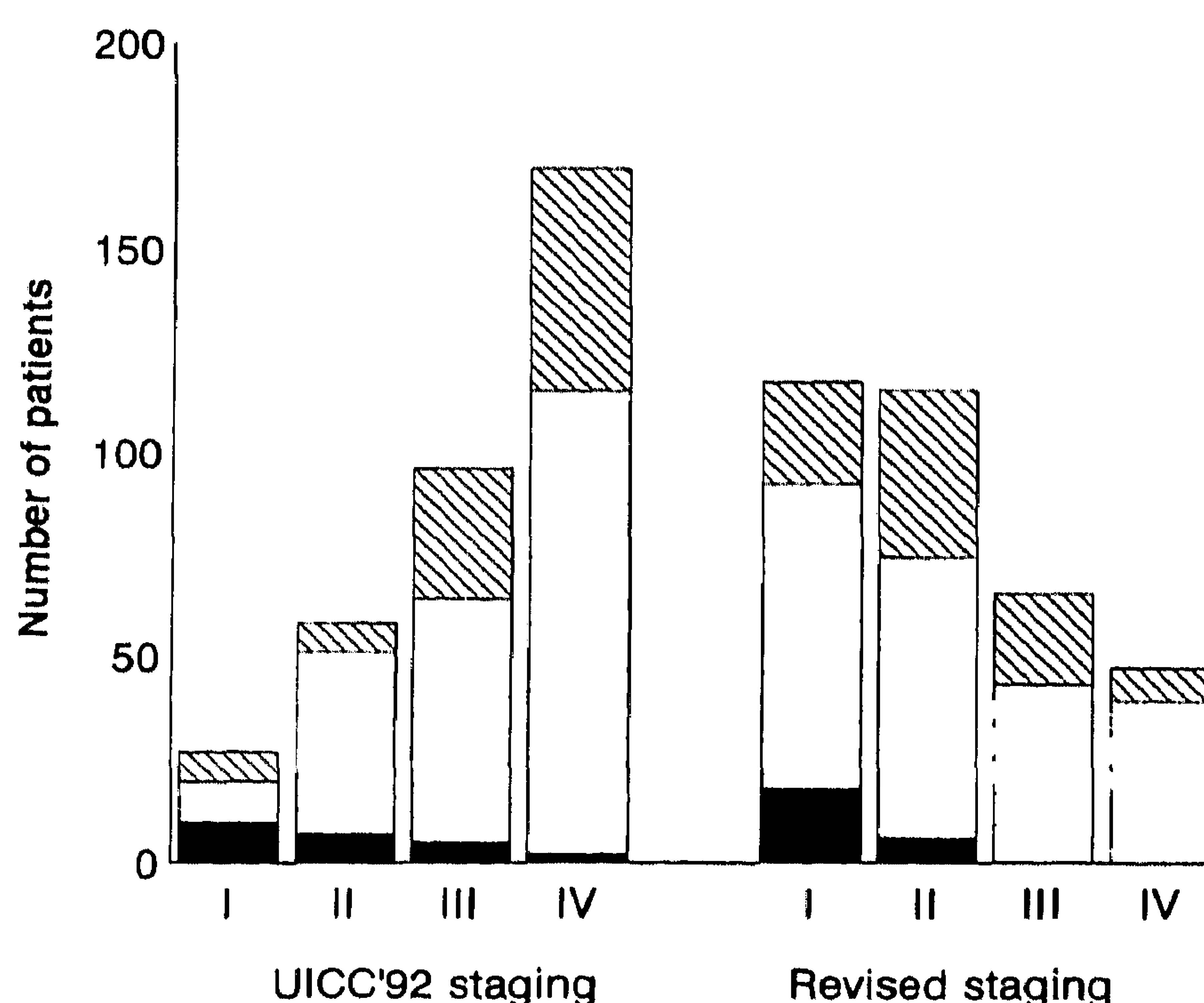


Figure 1. Treatment modality per stage UICC'92 and revised staging. ■ = surgery; □ = RT; ▨ = surgery + RT.

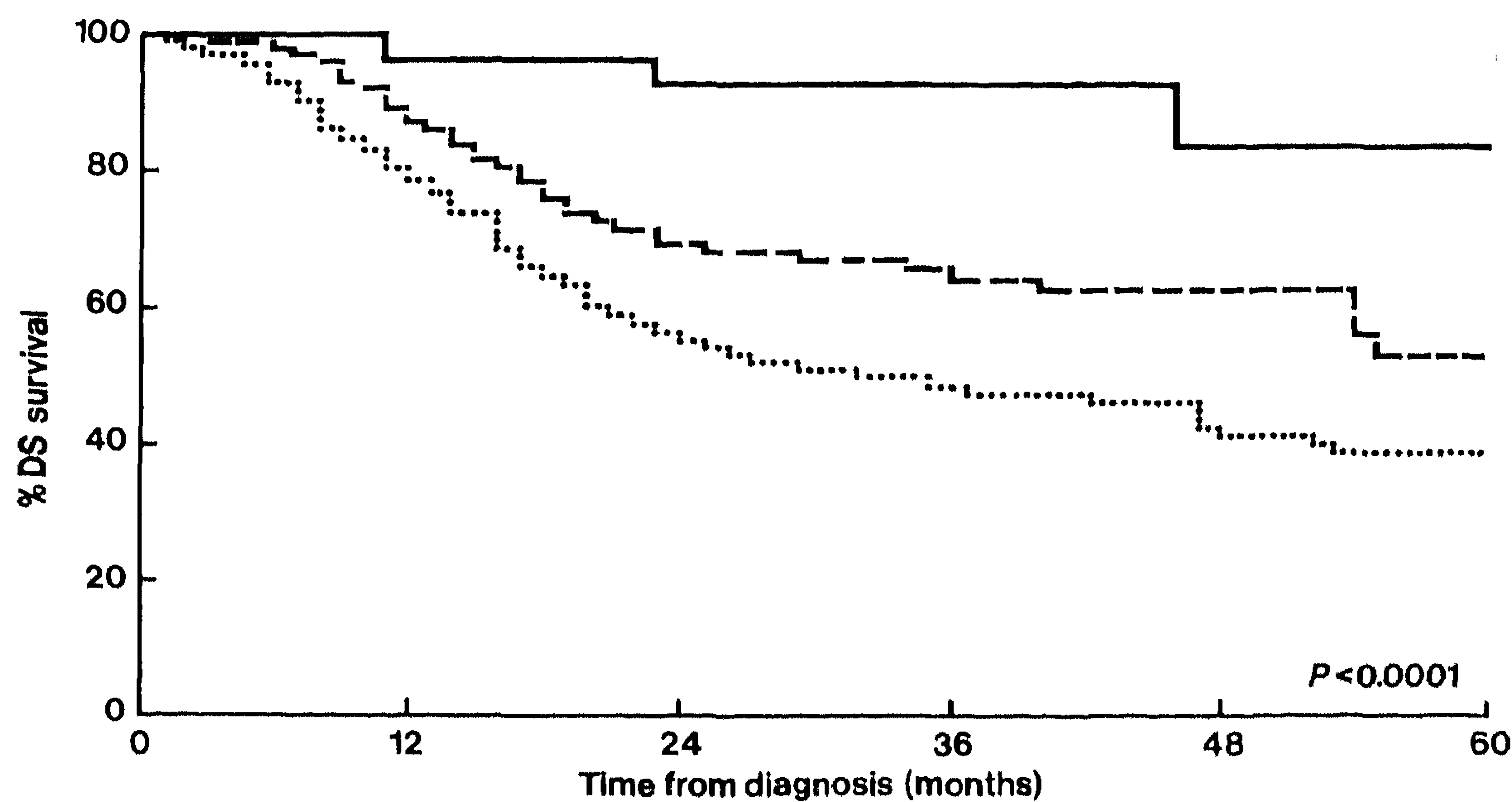


Figure 2. Disease-specific survival by treatment modality. — = 3/30 surgery; --- = 37/101 surgery+RT; ... = 120/231 RT.

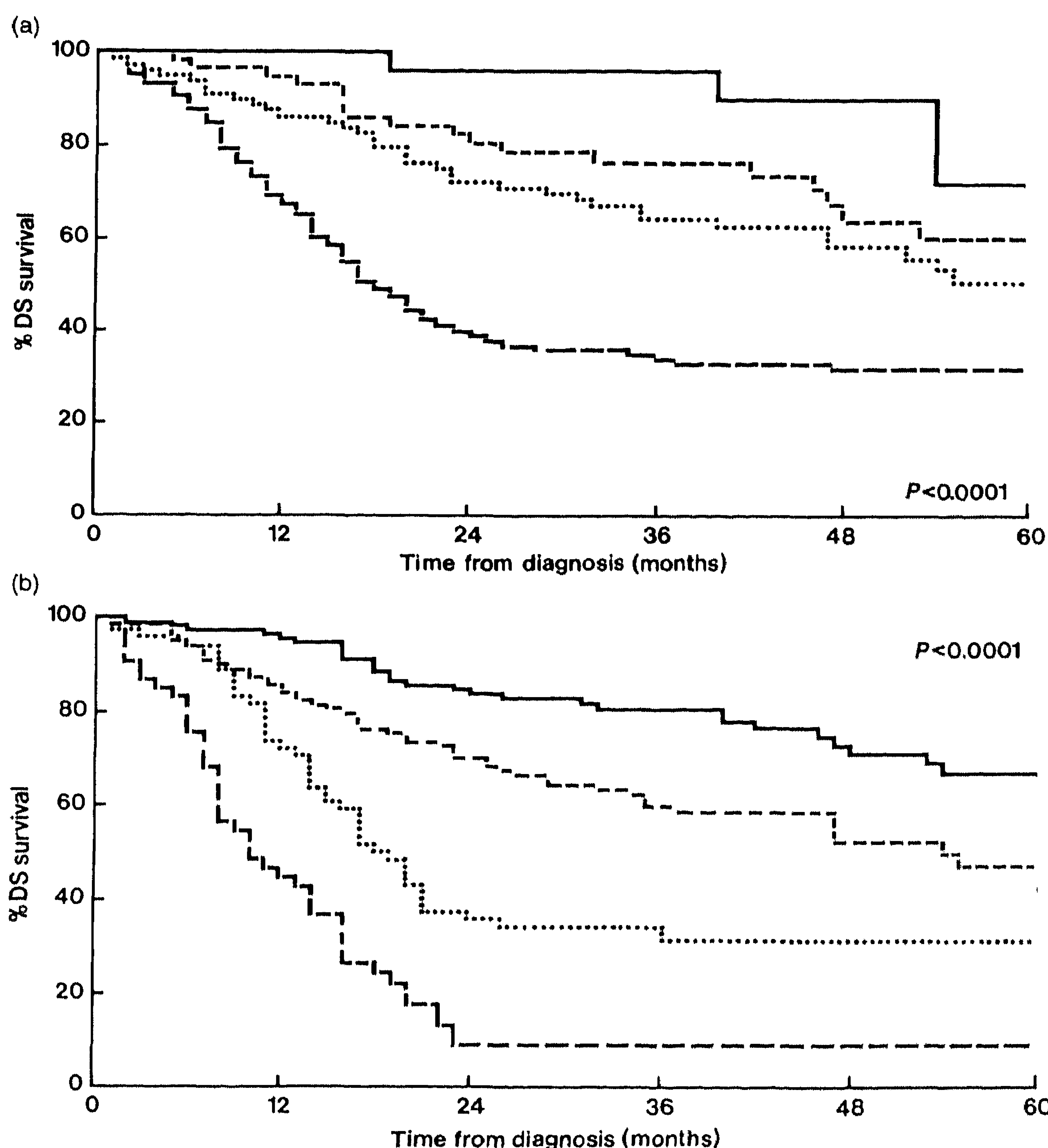


Figure 3. (a) Disease-specific survival by the UICC'92 staging system. — = 3/27 stage I; --- = 18/59 stage II; ... = 39/99 stage III; -.- = 112/182 stage IV. (b) Disease specific survival by the revised staging. — = 29/118 stage I; --- = 51/120 stage II; ... = 41/67 stage III; -.- = 46/54 stage IV.

oropharyngeal cancer were studied. Special attention has been given to factors influencing the disease-specific survival, loco-regional control and the relevance of a revised staging system.¹⁸ With respect to the latter, it could be observed that the distribution of patients in this revised staging system leads to a shift of approximately two-thirds of patients towards

stages I and II. Thus, according to the revised staging, tonsillar tumours, with the majority of patients in earlier stages, seem to form a favourable subgroup in the oropharynx. Moreover, the absence of tumours in the midline, previously identified as a favourable prognostic factor for survival,¹⁸ might further explain the better treatment results in tonsillar carcinoma.⁴⁻⁷

Table 2. Vital status at the end of the follow-up of 380 patients with tonsillar carcinoma

Alive, NED*	140
Alive with tumour	7
Dead, NED	55
Dead with tumour	176
Unknown	2

*No evidence of disease

when compared to most other subsites in the oropharynx.⁸⁻¹⁵

The clinical relevance of the revised system is also indicated by the distribution of treatment modalities over the stages: in the revised version surgery alone was used only in stages I-II and a steady increase of patients treated with radiotherapy alone was observed from stage I to IV. In contrast, in the UICC'92 system, seven patients in stage III and IV still received surgery as their only treatment modality.

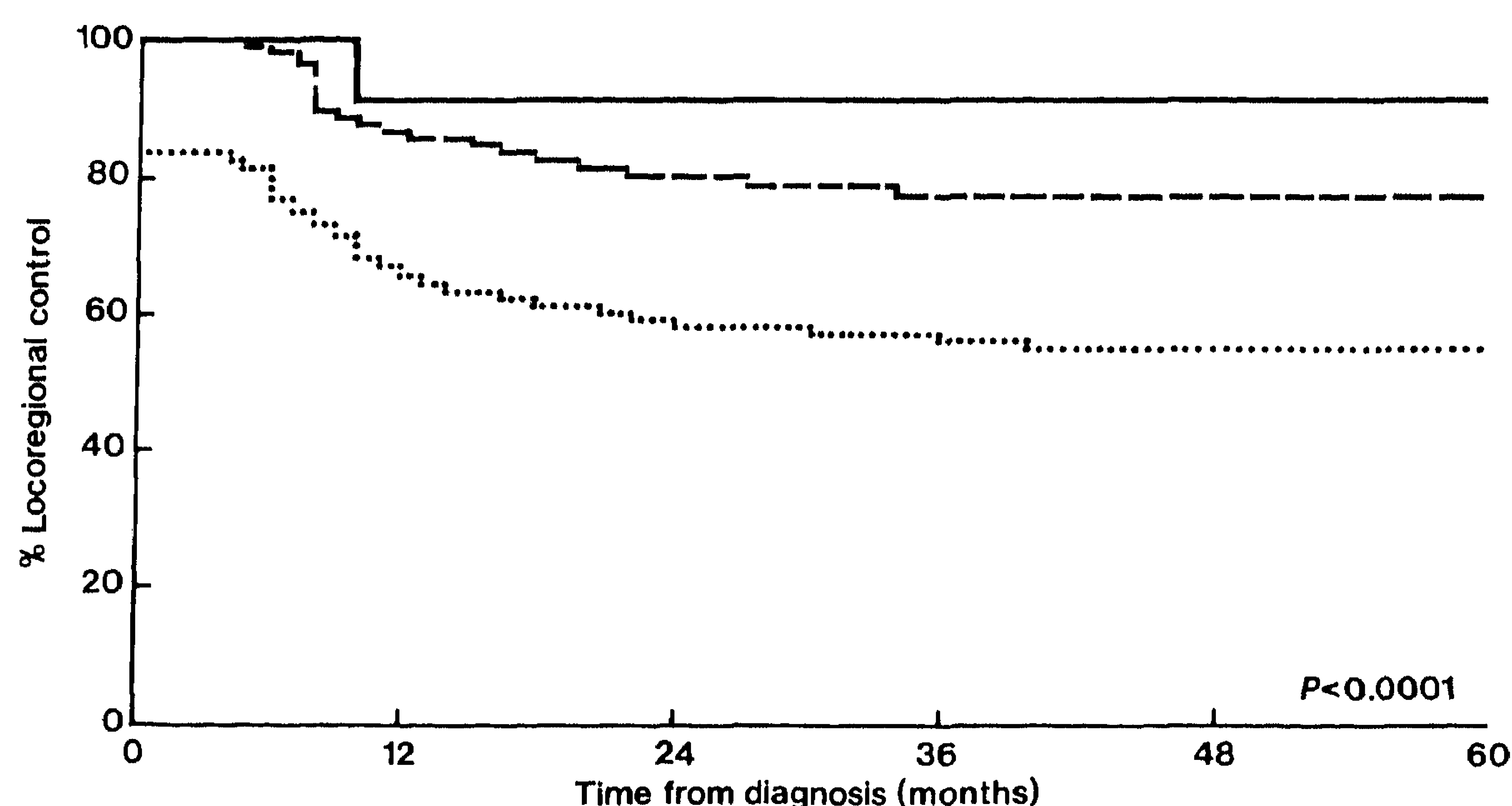
Also the range of the disease-specific survival and locoregional control in the four stages was wider in the revised staging compared to the UICC'92 system. However, multivariate analysis has shown a similar prognostic effect of both staging systems when locoregional control was taken as the end-point. These results are somewhat different from the outcome of the analysis of all patients with oropharyngeal carcinoma having survival as the end-point. In that case the revised staging seemed to be superior to the UICC'92 system.¹⁸ However, the revised system was optimized for disease-specific survival in that patient group, so an unbiased comparison with other staging systems can only be performed in an independent sample of patients. In testing the interaction of treatment and stage, the relatively small group of 30 patients treated with surgery alone, was omitted from the analysis. It is obvious that this subgroup selection on favourable prognostic parameters (low age, good performance status, wide margins) plays too great a role for meaningful comparison. Interestingly, the difference in locoregional control between radio-

therapy alone and combination treatment was not proven to be dependent on stage (interaction: $P = 0.073$), although it seems to be more clearly present in stage IV.

The importance of complete tumour regression at the end of treatment could be demonstrated clearly through the disappearance of significant differences between both groups when patients with residual disease were excluded. Once a complete remission is reached, as almost by definition readily obtained with initial surgery, the prognosis is quite favourable through all stages. For radiotherapy it is known that regression of tumour during the treatment and total clearance at the end of radiotherapy and 6 weeks later predict the tumour control very reliably.^{1,8,10,23,24} Upon identifying residual disease and excluding those patients from further comparison, similar control rates were obtained with both modalities.

The issue of selecting patients for surgery based on good performance status cannot be addressed in this study, since these data, as in many other series, were not available. As stated previously,¹⁷ the standardized checklists designed for this project only included well-defined, categorized basic data, that were likely to be present in all or almost all patients' records. Despite the obvious importance of host characteristics in choosing treatment and predicting survival,^{16,25,26} a systematic and structured inclusion of these items in patients' records and study questionnaires has not been widely adopted. In this particular study we do know that in many clinics primary radiotherapy was often the therapy of choice, particularly in the lower UICC'92 stages.

In conclusion, the revised staging provided a shift of patients with tonsillar carcinoma towards lower stages and a wider spread of survival and locoregional control curves, when compared to the UICC'92 system. In the multivariate analysis of the prognostic factors, the revised staging appeared to be comparable to the UICC'92 staging system, but not superior to it. Treatment results of the combination of surgery and radiotherapy were significantly better than those of radiotherapy alone, also when adjusted for stage. Whether this is

**Figure 4.** Locoregional control by treatment modality. — = 1/24 surgery; --- = 23/100 surgery + radiotherapy; ... = 96/226 radiotherapy.

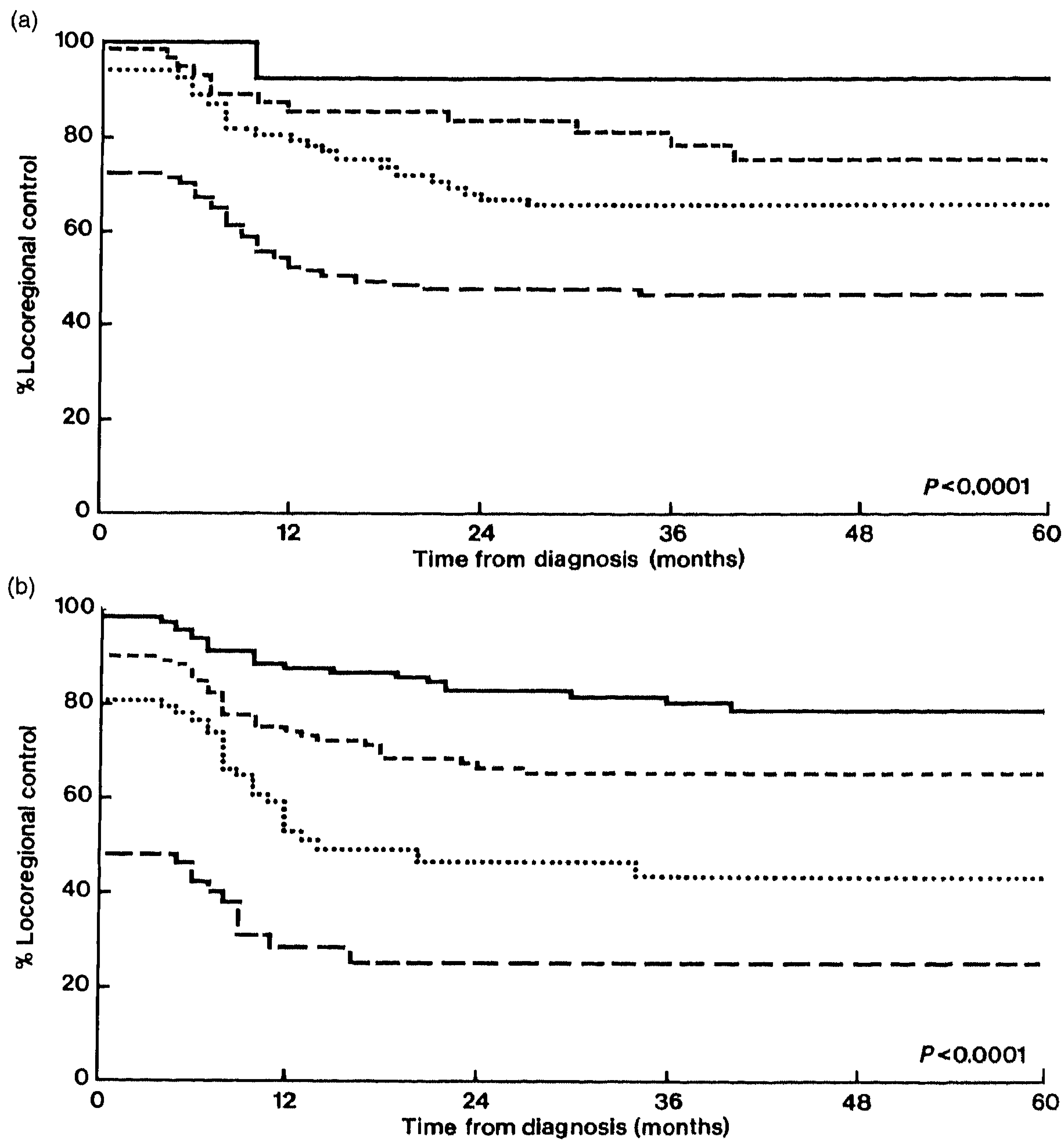


Figure 5. (a) Locoregional control by UICC'92 staging system. — = 2/27 stage I; --- = 12/59 stage II; ... = 32/99 stage III; - · - = 90/182 stage IV. (b) Locoregional control by the revised staging. — = 22/118 stage I; --- = 39/120 stage II; ... = 34/67 stage III; - · - = 38/54 stage IV.

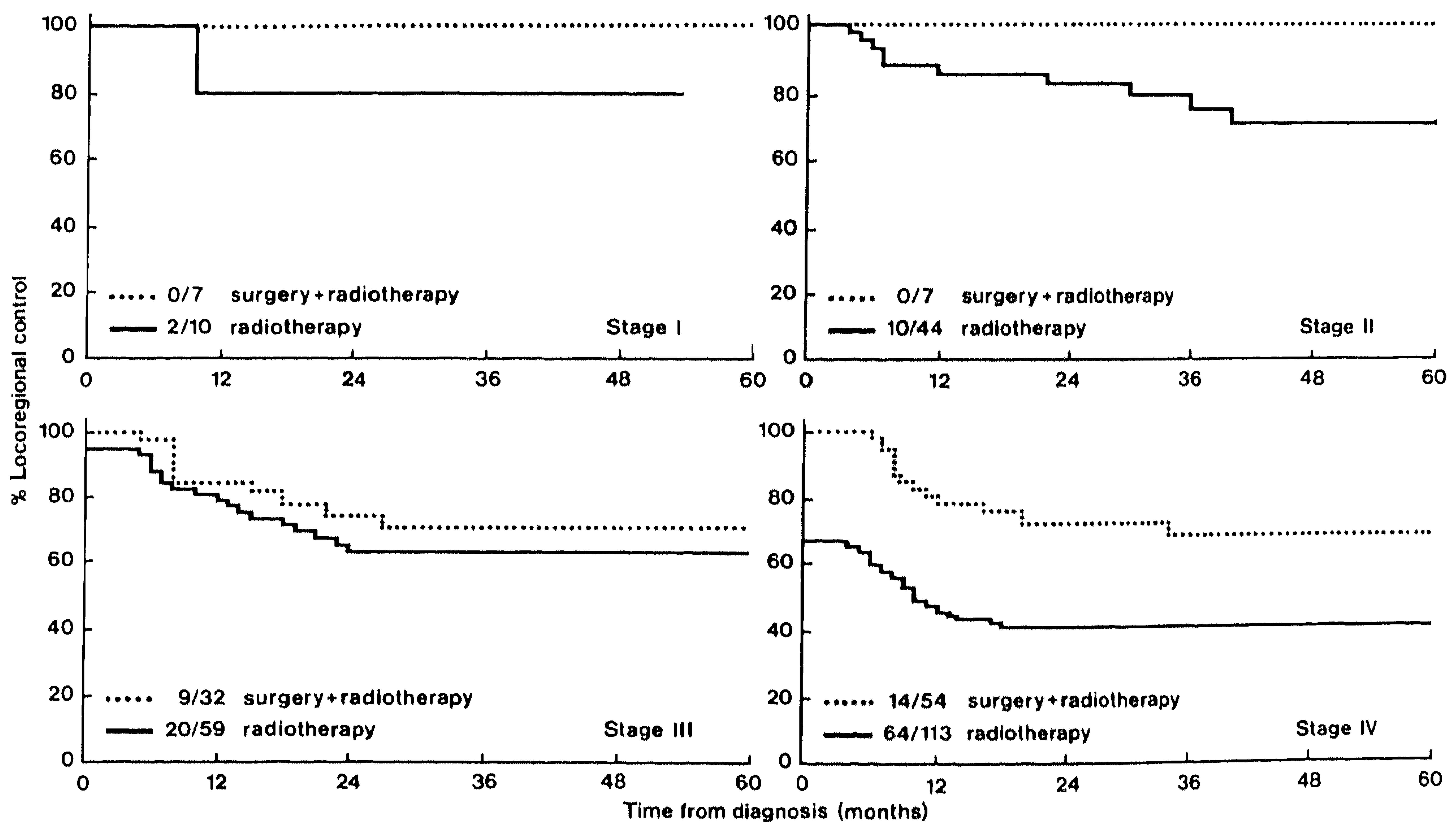


Figure 6. Locoregional control by treatment modality per UICC'92 stage.

due to the treatment modality itself, or to confounders thus far unidentified, is still open for discussion.

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